Osteoporosis International (2019) 30:2019–2025
https://doi.org/10.1007/s00198-019-05033-3

ORIGINAL ARTICLE

Parathyroid hormone independently predicts fracture, vascular events, and death in patients with stage 3 and 4 chronic kidney disease

S. Geng[1] · Z. Kuang[2] · P.L. Peissig[3] · D. Page[4] · L. Maursetter[5] · K.E. Hansen[5]

Received: 13 February 2019 / Accepted: 22 May 2019 / Published online: 31 May 2019

Abstract

Summary Doctors do not know whether treatment of high parathyroid hormone levels is linked to better outcomes in their patients with kidney disease. In this study, lower parathyroid hormone levels at baseline were linked to lower risk of fracture, vascular events, and death in people with kidney disease.

Purpose Chronic kidney disease (CKD) affects ~ 20% of older adults, and secondary hyperparathyroidism (HPT) is a common condition in these patients. To what degree HPT predicts fractures, vascular events, and mortality in pre-dialysis CKD patients is debated. In stage 3 and 4 CKD patients, we assessed relationships between baseline serum PTH levels and subsequent 10-year probabilities of clinical fractures, vascular events, and death.

Methods We used Marshfield Clinic Health System electronic health records to analyze data from adult CKD patients receiving care between 1985 and 2013, and whose PTH was measured using a second-generation assay. Covariates included PTH, age, gender, tobacco use, vascular disease, diabetes, hypertension, hyperlipidemia, obesity, GFR, and use of osteoporosis medications.

Results Five thousand one hundred eight subjects had a mean age of 68 ± 17 years, 48% were men, and mean follow-up was 23 ± 10 years. Fractures, vascular events, and death occurred in 18%, 71%, and 56% of the cohort, respectively. In univariate and multivariate models, PTH was an independent predictor of fracture, vascular events, and death. The hazards of fracture, vascular events and death were minimized at a baseline PTH of 0, 69, and 58 pg/mL, respectively.

Conclusions We found that among individuals with stage 3 and 4 CKD, PTH was an independent predictor of fractures, vascular events, and death. Additional epidemiologic studies are needed to confirm these findings. If a target PTH range can be confirmed, then randomized placebo-controlled trials will be needed to confirm that treating HPT reduces the risk of fracture, vascular events, and death.

Keywords Chronic kidney disease · Fractures · Mortality · Secondary hyperparathyroidism · Vascular events

✉ K.E. Hansen
keh@medicine.wisc.edu

S. Geng
sgeng@cs.princeton.edu

Z. Kuang
kuangz@stanford.edu

P.L. Peissig
peissig.peggy@marshfieldclinic.org

D. Page
page@biostat.wisc.edu

L. Maursetter
lmaursetter@medicine.wisc.edu

[1] Department of Computer Science, Princeton University, Princeton, NJ, USA

[2] Computer Science Department, Stanford University, Stanford, CA, USA

[3] Center for Computational and Biomedical Informatics, Marshfield Clinic Research Institute, Marshfield, WI, USA

[4] Department of Biostatistics and Medical Informatics, Department of Computer Sciences, University of Wisconsin-Madison, Madison, WI, USA

[5] Department of Medicine, University of Wisconsin School of Medicine & Public Health, Mailbox 4124, Medical Foundation Centennial Building, 1685 Highland Avenue, Madison, WI 53705-2281, USA

Introduction

CKD affects one in five older adults [1] and 14% of the general population [2]. CKD causes more deaths per year than breast or prostate cancer [2]. Medicare spends nearly one-fifth of its budget on CKD patient care, due to excess vascular events, fractures, infections, and subsequent premature death [3] compared with patients without CKD. Indeed, patients > 65 years old with CKD have a higher prevalence of cardiovascular disease compared to individuals of the same age without CKD (70% vs. 35%) [2].

Secondary hyperparathyroidism (HPT) affects nearly all stage 5 (dialysis) CKD patients and over half of stage 3–4 CKD patients [4–6]. The pathogenesis of hyperparathyroidism is well established [7]. Declining renal $1,25(OH)_2D$ synthesis leads to reduced intestinal calcium absorption and lower ionized serum calcium levels. To maintain normocalcemia, the parathyroid glands released parathyroid hormone (PTH), which upregulates renal $1,25(OH)_2D$ synthesis to increase calcium absorption, and stimulates osteoclastic bone resorption to liberate skeletal calcium into the bloodstream.

Because HPT increases osteoclastic bone resorption, prolonged HPT would be expected to reduce BMD and increase the probability of fractures. In a literature review, we found only four cross-sectional studies [5, 8–10] in 356 individuals that evaluated the relationship between PTH and bone mineral density (BMD) in patients with stage 3–4 CKD. Three of four studies identified a relationship between PTH and BMD, suggesting that treatment of HPT would increase BMD and reduce risk of fractures. We found weak evidence suggested that treating HPT improved bone mineral density (2 trials, 62 subjects) [11, 12] and no trials testing whether treatment of HPT reduced the risk of fracture. Likewise, we found no trials that evaluated whether treating HPT reduced the risk of vascular events or death.

Based on expert opinion and observational studies, the National Kidney Foundation published guidelines on how to manage HPT. The 2003 guidelines [13] suggested specific PTH targets to achieve, depending on the stage of kidney disease. However, the 2009 National Kidney Foundation guidelines [7] acknowledged that target PTH levels were based on expert opinion, rather than randomized clinical trials. Because vitamin D analogs can raise serum calcium and phosphorus and might promote vascular calcification, the 2017 National Kidney Foundation guidelines [14] reserved treatment for stage 3–4 CKD patients with severe and progressive hyperparathyroidism; specific PTH targets were not recommended.

In summary, the potential harm from the use of vitamin D and its analogs, and lack of clinical trials proving the benefits of such therapy, have led to uncertainty about whether to treat HPT in stage 3 and 4 CKD patients. We utilized the Marshfield Clinic Health System (MCHS) data repository to evaluate relationships between serum PTH levels and clinical fractures, vascular events, and mortality in patients with stage 3 and 4 chronic kidney disease. Our objectives were to (1) evaluate whether PTH was an independent predictor of these events, and (2) seek an optimal PTH level that minimized these three adverse clinical outcomes. We hypothesized that higher PTH levels would be associated with greater probability of fractures, vascular events, and death, compared with lower PTH levels.

Methods

We utilized electronic health records of patients within the MCHS data repository from a collection period spanning 28 years (1985 to 2013). The database includes patients' demographic characteristics, medical conditions, laboratory results, fractures, imaging results, and medication use. We included patients who were (1) ≥ 21 years old, (2) had a mean GFR < 60 mL/min during the baseline year based on the average of at least 2 measures, (3) had at least two parathyroid hormone levels measured during the baseline year during outpatient clinic visits, and (4) subsequently received medical care at Marshfield Clinic for at least 2 years, prior to November 2013. We excluded patients on dialysis and patients with primary hyperparathyroidism. We further excluded patients who had undergone parathyroidectomy, a procedure largely restricted to dialysis patients.

As in other medical centers, the PTH assay used at the Marshfield Clinic Laboratory changed several times over the span of 30 years. First generation PTH assays measured PTH fragments that accumulated in renal failure but were devoid of biologic activity [15]. Third generation PTH assays did not detect PTH7-84 fragments [15]. Currently, the second generation assay is used in the vast majority of medical centers [16]. To make our study results most relevant to current clinical practice, we limited our analysis to subjects whose PTH was measured using a 2nd generation assay. Such 2nd generation assays were first used at MCHS in February 1997.

Co-variates in multiple variable models were chosen based on their known association with the risk of fracture, vascular events, and death. Thus, we included age (≤59, 60–69, 70–79, and ≥ 80 years old), gender, tobacco use, vascular disease, diabetes, hypertension, hyperlipidemia, obesity, GFR, and osteoporosis medication as covariates. At least two ICD-9 coded clinic encounters within a 24-month interval were required to denote the presence of diabetes, hypertension, or hyperlipidemia, as described elsewhere [17, 18]. We used ICD-9 codes designating specific skeletal fracture sites known to reflect osteoporotic fracture including hip (ICD-9820–822), wrist (ICD-9813), humerus (ICD-9812), and vertebral (ICD-9805) fractures. We also used ICD-9 codes to denote vascular events. We required that at least two clinical encounters noted

the ICD-9 code prior to counting the vascular event, since "ruling out" such an event was often used to support the need for imaging (e.g., head CT scan to rule out stroke).

Statistical analysis

We analyzed predictors of three clinical outcomes (fracture, vascular events, death) occurring after parathyroid hormone measurement, using the mean of two or more baseline PTH values. First, we used survival tree models [19] with the tenfold cross-validation method [20] to identify the PTH level at which the probability of each clinical outcome was minimized. In the full survival tree model, we used all covariates, while in the second or reduced model, we employed the mean PTH level alone. We then applied Cox proportional hazard models using each selected PTH cutpoint, to confirm the survival tree models indicating the PTH level at which the probability of each outcome was minimized. Herein, we only report the models using the significant cutpoints. We used Cox proportional hazard ratios and Kaplan-Meier survival curves to evaluate the risks of each clinical outcome, in patients with PTH below and above the "optimal" level identified by survival tree and tenfold cross-validation models. Our multivariate models controlled for age, gender, tobacco use, diabetes, hypertension, hyperlipidemia, vascular disease, obesity, GFR, bisphosphonate, and other bone-active medications [21–23]. We performed a further sub-analysis to assess whether the optimal PTH level differed between patients with stage 3 and stage 4 CKD. We used version 3.2.3 of "R" (The R Project for Statistical Computing, http://www.r-project.org) for all statistical analyses.

Results

We initially identified 7594 potentially eligible subjects who received care at MCHS between 1985 and 2013. Among these subjects, 5108 (67%) had PTH measured during the baseline year using a 2nd-generation PTH assay and were included in the current study. The final cohort of 5108 patients were 68 ± 17 years old, 48% were men, and they received care at MCHS for 23 ± 10 years (Table 1). Among the cohort, 18% sustained clinical fractures, 71% experienced vascular events, and 56% died. We did not include race, body mass index, denosumab, or teriparatide as covariates due to lack of records regarding these data (race, body mass index) or too few individuals with the characteristic (use of denosumab or teriparatide). The 2010 United States Census estimated that ~ 19,000 people lived in Marshfield, Wisconsin, and the vast majority (~ 95%) were Caucasian, suggesting that our cohort was largely Caucasian [24]. We had no missing data for age, gender, diabetes, hypertension, hyperlipidemia, coronary artery disease, peripheral vascular disease, bisphosphonate, estrogen, or testosterone therapy.

PTH was significantly associated with fractures, vascular events, and death in univariate models (Table 2). In multivariate models, PTH remained a significant predictor of fracture, along with age, gender, vascular disease, and osteoporosis therapy (Table 3). Likewise, PTH remained an independent predictor of vascular events in a multiple variable model, along with age, gender, diabetes, obesity, and GFR (Table 3). Finally, in multiple variable models predicting death, PTH was once again an independent predictor along with age, gender, vascular disease, diabetes, hypertension, hyperlipidemia, obesity, and GFR (Table 3).

We investigated the baseline PTH value at which fracture, vascular events, and deaths was lowest. In these analyses, we used survival tree models with tenfold cross validation. Initial analyses suggested that the odds of fracture was lowest when baseline PTH values were 101 pg/mL. However, there was no significant difference between the slope of the curve for fracture risk, when comparing the odds of fracture in subjects with baseline PTH levels above and below 101 pg/mL. Instead, graphing of data showed that the odds of fracture rose in parallel with rising PTH (Fig. 1). In the fracture model using PTH as a continuous variable, PTH remained a significant independent risk factor ($p = 0.042$). In conclusion, a PTH level of zero was associated with the lowest probability of subsequent fracture. In this sensitivity analysis, the probability of vascular events was lowest at a baseline PTH of 69 pg/mL (Fig. 2). The probability of death was minimized when baseline PTH was 58 pg/mL (Fig. 2). Table 3 provides the hazards of fracture, vascular events, and death, using the PTH cutpoints identified in models.

Probability of fracture, vascular events, and death by stage of CKD

We performed a sensitivity analysis to determine whether the optimal PTH cutpoint differed, based on stage of CKD. In this analysis, we grouped patients into those with an average GFR ≥ 30 mL/min ($n = 3923$) and a GFR < 30 mL/min ($n = 1185$) during the baseline year. In these analyses, we found no optimal PTH level that reduced the risk of fracture. In subjects with a GFR ≥ 30 mL/min, a PTH of 69 pg/mL was associated with the lowest risk of vascular events. In subjects with a GFR < 30 mL/min, a PTH of 58 pg/mL was associated with lowest risk of death. In the other subgroups, we found no clear cutpoint in PTH associated with clinical outcomes.

Table 1 Subject characteristics

		7594 subjects	5108 subjects
Clinical	Age, years	68 ± 13	68 ± 17
	Male gender	3418 (45%)	2433 (48%)
	Tobacco use	4129 (54%)	3031 (59%)
	Duration of care at Marshfield Clinic	25 ± 15 years	23 ± 10 years
Prevalence of comorbidities	Coronary artery or peripheral vascular disease	4981 (66%)	3644 (64%)
	Diabetes	3875 (51%)	2725 (53%)
	Hypertension	6793 (89%)	4730 (93%)
	Hyperlipidemia	3606 (47%)	2671 (52%)
	Obesity	3141 (41%)	2350 (46%)
Labs	GFR, mL/min	39 ± 16	35 ± 13
	PTH, pg/mL	98 ± 91	105 ± 100
Medication	Bisphosphonates	–	709 (14%)
	Denosumab or teriparatide	–	113 (2%)
	Estrogen, raloxifene, testosterone	–	519 (10%)
Outcomes	Fractures	–	921 (18%)
	Vascular events	–	3644 (71%)
	Death	–	2865 (56%)

Discussion

KDIGO recommends specific PTH levels to achieve in dialysis patients [14], based on epidemiologic studies demonstrating that PTH levels < 2 and > 9 times the normal range are associated with cardiovascular and all-cause mortality [25, 26]. However, KDIGO found insufficient data to define the optimal PTH level in pre-dialysis CKD patients. We conducted the current study in order to evaluate the relationship between baseline PTH levels and long-term risk of fractures, vascular events, and death in a large cohort of stage 3–4 CKD patients who were medically homed at MCHS. In our study, PTH was an independent risk factor in multiple variable models predicting fracture, vascular events, and death. In survival tree models with tenfold cross-validation, fracture risk was lowest at a PTH level of zero, and steadily rose in concert with a rising PTH. By contrast, the risk of vascular events and death were lowest when baseline PTH levels were 69 and 58 pg/mL, respectively.

In a literature review, we found four cross-sectional studies [5, 8–10] in 356 individuals that evaluated the relationship between PTH and bone mineral density (BMD) in patients with pre-dialysis CKD. In the first study, PTH was inversely associated with 33% radius ($r - 0.701$, $p < 0.01$) but not with spine BMD in 69 patients with CKD [8]. Intact PTH values were 78 ± 18 pg/mL in stage 3, 123 ± 21 pg/mL in stage 4, and 312 ± 39 pg/mL in stage 5 (GFR 9–15 mL/min) patients [8]. In a second study [9] of 113 patients with creatinine > 1.5 mg/dL, those with PTH > 2 times upper normal limit had lower spine, hip, and total body BMD, compared with CKD patients with normal PTH; patients' PTH values were not reported. A third study [10] in 85 individuals with creatinine > 1.5 mg/dL and PTH values of 127 ± 113 pg/mL, researchers found no correlation between PTH and radius BMD at baseline, or between PTH and the 1-year change in radius BMD. In a fourth study [5] of 89 patients with stage 3–4 CKD and median PTH values of 76 (9–283) ng/L, the log of PTH was inversely associated with the log of total hip BMD, in univariate and multivariate models. Thus, three of four studies identified a relationship between PTH and BMD, suggesting that treatment of HPT would increase BMD and reduce risk of fractures. However, we found only weak evidence suggesting that treating HPT-improved bone mineral density (2 trials, 62 subjects) [11, 12] and no clinical trials assessing whether treatment of HPT reduces the risk of fractures.

Table 2 Univariate relationship between baseline parathyroid hormone levels and hazards of fracture, vascular events, and death[a]

Fracture		Vascular events		Death	
HR[b] (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95%CI)	*p* value
1.001 (1.001, 1.002)	0.039	1.001 (1.001, 1.002)	< 0.001	1.002 (1.001, 1.002)	< 0.001

[a] Parathyroid hormone was analyzed as a continuous variable in univariate models

[b] HR indicates the hazard ratio with its 95% confidence interval

Table 3 Multiple covariate models predicting hazard ratios for fracture, vascular events, and death in 5108 patients with 2nd-generation PTH values above and below thresholds

		Fracture		Vascular events		Death	
Covariates		HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95%CI)	*p* value
Clinical	Age ≤ 59 years	0.47 (0.36, 0.63)	< 0.001	0.44 (0.39, 0.49)	< 0.001	0.30 (0.26, 0.34)	< 0.001
	Age 60–69	0.54 (0.42, 0.69)	< 0.001	0.56 (0.50, 0.62)	< 0.001	0.40 (0.36, 0.45)	< 0.001
	Age 70–79	0.75 (0.60, 0.92)	0.006	0.70 (0.63, 0.77)	< 0.001	0.58 (0.52, 0.64)	< 0.001
	Age ≥ 80 years	referent		referent		referent	
	Male gender	0.69 (0.58, 0.84)	< 0.001	1.28 (1.18, 1.38)	<0.001	1.26 (1.16, 1.38)	< 0.001
	Tobacco Use	0.93 (0.79, 1.11)	0.427	1.07 (0.99, 1.16)	0.069	1.01 (0.93, 1.10)	0.752
Comorbidities	Vascular disease	1.80 (1.44, 2.26)	< 0.001	–	–	1.61 (1.44, 1.79)	< 0.001
	Diabetes	1.18 (1.00, 1.40)	0.055	1.29 (1.19, 1.39)	< 0.001	1.23 (1.13, 1.33)	< 0.001
	Hypertension	1.28 (0.84, 1.94)	0.249	1.05 (0.89, 1.23)	0.596	0.75 (0.64, 0.88)	< 0.001
	Hyperlipidemia	0.99 (0.83, 1.17)	0.887	0.99 (0.93, 1.07)	0.879	0.80 (0.74, 0.86)	< 0.001
	Obesity	0.89 (0.75, 1.07)	0.212	1.12 (1.04, 1.21)	0.003	0.91 (0.84, 0.99)	0.029
Labs	GFR, mL/min	1.00 (0.99, 1.00)	0.268	0.99 (0.99, 0.99)	< 0.001	0.98 (0.98, 0.98)	< 0.001
	PTH < cutpoint	0.95 (0.78, 1.15)[a]	0.605	1.11 (1.00, 1.23)[b]	0.058	1.05 (0.89, 1.25)[b]	0.546
	PTH > cutpoint	1.16 (0.93, 1.45)[a]	0.195	1.18 (1.09, 1.27)[b]	< 0.001	1.19 (1.09, 1.30)[b]	< 0.001
Meds	Bisphosphonates	1.65 (1.35, 2.01)	<0.001	1.00 (0.90, 1.11)	0.988	1.09 (0.98, 1.22)	0.126
	Other[c]	1.50 (1.22, 1.85)	< 0.001	0.93 (0.83, 1.03)	0.176	0.89 (0.79, 1.01)	0.068

[a] Initial analyses suggested that the PTH cutpoint for reduced hazard of fracture was 101 pg/mL. However, there was no significant difference between the slope of the curve for fracture risk, when comparing odds of fracture in subjects with baseline PTH levels above and below a PTH value of 101 pg/mL. Instead, graphing of data showed that the odds of fracture rose in association with rising PTH. In the fracture model using PTH as a continuous variable, PTH remained a significant independent risk factor ($p = 0.042$)

[b] The PTH cutpoint was 69 pg/mL for vascular events and 58 pg/mL for death

[c] Other medications included estrogen, raloxifene, and testosterone

We found three studies that explored the relationship between PTH and subsequent vascular events or death in pre-dialysis CKD patients. A retrospective study of veterans with stage 3 and 4 CKD found that PTH was significantly higher in 48 veterans with cardiovascular events, compared to 148 without such events (156 ± 107 vs. 109 ± 87 pg/mL, $p = 0.003$) [27]. The odds of sustaining a cardiovascular event were 1.3

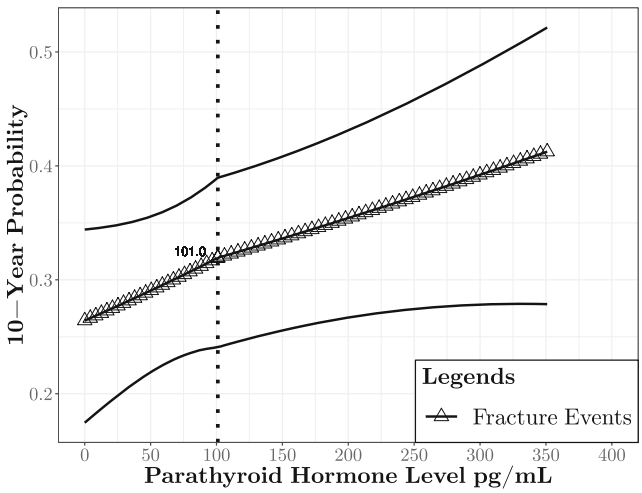

Fig. 1 Ten-year probability of fractures, based on baseline parathyroid hormone levels. The figure demonstrates a linear relationship between baseline parathyroid hormone levels and ten-year probability of clinical fractures. While there was a small inflection point at a PTH value of 101 pg/mL, there was no significant difference between the slope of the curve for fracture risk, when comparing odds of fracture in subjects with baseline PTH levels above and below a PTH value of 101 pg/mL. Instead, the hazards of fracture rose steadily with increasing PTH values

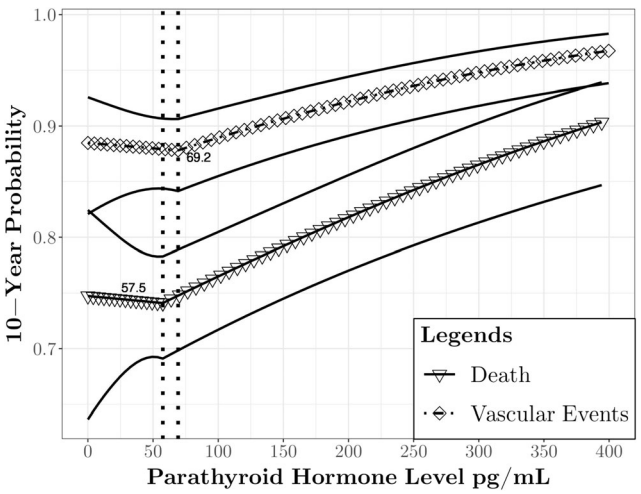

Fig. 2 Ten-year probability of vascular events and death, based on baseline parathyroid hormone levels. The figure demonstrates that hazards of vascular events and death were lowest at PTH values of 69 and 59 ng/mL, respectively

(95% confidence interval, 1.03, 1.55) for every 50 pg/mL increase in PTH. The study suggests that treating HPT in stage 3–4 CKD patients might reduce the risk of vascular events, thereby prolonging life. However, among nearly 4000 participants of the Chronic Renal Insufficiency Cohort, baseline PTH levels did not predict vascular events or death, whereas baseline FGF23 levels did predict these clinical outcomes [28, 29]. We found no clinical trials demonstrating that treatment of HPT reduced vascular events or death in stage 3–4 CKD patients.

Among patients with primary hyperparathyroidism, researchers have evaluated the relationship between baseline PTH levels and subsequent risk of fractures, vascular events, and death. In the Parathyroid Epidemiology and Audit Research Study (PEARS), 1683 individuals with mild primary hyperparathyroidism who did not undergo parathyroidectomy were monitored for adverse outcomes, and rates were compared with those in age and gender-matched population of individuals living in the same region [30, 31]. In PEARS, baseline PTH was associated with fractures, cardiovascular disease, and all-cause mortality. Interestingly, PTH levels in patients with primary hyperparathyroidism have been linked to higher systolic blood pressure, increased pulse wave velocity, and greater left ventricular mass [32]. In unselected patients undergoing cardiac catheterization, higher PTH levels were associated with both the number and severity of coronary artery occlusion [33].

Vascular smooth muscle and endothelial cells express receptors for PTH and PTH-related protein [34]. In ex vivo experiments using femoral principle nutrient arteries [35], the addition of PTH and PTH-related peptide promoted vasodilation. To our knowledge, there is no direct data that PTH levels rise to compensate for poor blood flow to the skeleton or internal organs. Further studies are needed to understand whether PTH is secreted in response to poor blood flow to bones or vital organs.

We acknowledge that our study has both strengths and limitations. We analyzed a large number of subjects' electronic health records. We controlled for covariates known to influence the risk of clinical outcomes. However, the nature of this epidemiologic study can only suggest, not prove, a causal relationship between PTH values and clinical outcomes. Additionally, we could not determine whether low PTH values resulted from excess calcium intake, vitamin D therapy, or other factors. We had no information on why PTH was measured in subjects, or whether results prompted a specific intervention. Based on census data, our study contained very few non-Caucasian subjects. Body mass index was not universally recorded until 2005 at MCHS so instead, we used the less precise diagnosis of "obesity" as a covariate. We did not measure FGF23 levels, which were associated with vascular events and death in participants of the Chronic Renal Insufficiency Cohort [28, 29]. We did not include serum calcium and phosphorus levels in our models. Finally, we cannot determine whether fractures were due to skeletal fragility, as the circumstances leading fractures were not available via electronic health record search terms.

In conclusion, one in five older adults has CKD and most of these patients develop secondary hyperparathyroidism. Limited data exists on the relationship between PTH and clinical outcomes in CKD stage 3 and 4 patients. Additionally, there is no direct evidence from randomized, placebo-controlled trials to confirm that treatment of secondary hyperparathyroidism reduces fractures, vascular events, or death. We undertook this study to evaluate the relationship between PTH and subsequent risk of fractures, vascular events, and death. We found that PTH was an independent predictor of all three adverse clinical outcomes. We also found that lower PTH was associated with a lower probability of all outcomes. Given the limitations of our study, it is important to verify these findings in another database. If additional studies confirm a proposed target PTH level at which fractures, vascular events, and death are reduced, then randomized clinical trials will be needed, to verify that treatment of HPT improves the health of CKD patients.

Acknowledgments We thank Bryan Robeson, Technical Manager at Marshfield Clinic Laboratory for supplying information on the parathyroid assays used at Marshfield Clinic.

Compliance with ethical standards

Conflict of interest None.

References

1. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS (2007) Prevalence of chronic kidney disease in the United States. Jama 298:2038–2047
2. National Institute of Diabetes and Digestive and Kidney Diseases (2016) kidney disease statistics for the United States. Accessed November 27, 2018
3. Saran R, Li Y, Robinson B et al (2015) US renal data system 2014 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 66(Svii):S1–S305
4. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, Andress DL (2007) Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int 71: 31–38
5. Stavroulopoulos A, Porter CJ, Roe SD, Hosking DJ, Cassidy MJ (2008) Relationship between vitamin D status, parathyroid hormone levels and bone mineral density in patients with chronic kidney disease stages 3 and 4. Nephrology (Carlton) 13:63–67
6. Ramos AM, Albalate M, Vazquez S, Caramelo C, Egido J, Ortiz A (2008) Hyperphosphatemia and hyperparathyroidism in incident chronic kidney disease patients. Kidney Int Suppl 74:S88–S93
7. (2009) KDIGO clinical practice guideline for the diagnosis, evaluation, prevention and treatment of Chronic Kidney Disease-Mineral

and Bone Disorder(CKD-MBD). Kidney Int Suppl (113):S1–130 https://doi.org/10.1038/ki.2009.188
8. Bianchi ML, Colantonio G, Montesano A, Trevisan C, Ortolani S, Rossi R, Buccianti G (1992) Bone mass status in different degrees of chronic renal failure. Bone 13:225–228
9. Rix M, Andreassen H, Eskildsen P, Langdahl B, Olgaard K (1999) Bone mineral density and biochemical markers of bone turnover in patients with predialysis chronic renal failure. Kidney Int 56:1084–1093
10. Tsuchida T, Ishimura E, Miki T, Matsumoto N, Naka H, Jono S, Inaba M, Nishizawa Y (2005) The clinical significance of serum osteocalcin and N-terminal propeptide of type I collagen in predialysis patients with chronic renal failure. Osteoporos Int 16: 172–179
11. Przedlacki J, Manelius J, Huttunen K (1995) Bone mineral density evaluated by dual-energy X-ray absorptiometry after one-year treatment with calcitriol started in the predialysis phase of chronic renal failure. Nephron 69:433–437
12. Rix M, Eskildsen P, Olgaard K (2004) Effect of 18 months of treatment with alfacalcidol on bone in patients with mild to moderate chronic renal failure. Nephrol Dial Transplant 19:870–876
13. (2003) K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 42:S1–S201
14. KDIGO (2017) Clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl 7:1–59
15. Gao P, D'Amour P (2005) Evolution of the parathyroid hormone (PTH) assay–importance of circulating PTH immunoheterogeneity and of its regulation. Clin Lab 51:21–29
16. Herberth J, Monier-Faugere MC, Mawad HW, Branscum AJ, Herberth Z, Wang G, Cantor T, Malluche HH (2009) The five most commonly used intact parathyroid hormone assays are useful for screening but not for diagnosing bone turnover abnormalities in CKD-5 patients. Clin Nephrol 72:5–14
17. Magnan EM, Palta M, Johnson HM, Bartels CM, Schumacher JR, Smith MA (2015) The impact of a patient's concordant and discordant chronic conditions on diabetes care quality measures. J Diabetes Complicat 29:288–294
18. Johnson HM, Bartels CM, Thorpe CT, Schumacher JR, Pandhi N, Smith MA (2015) Differential diagnosis and treatment rates between systolic and diastolic hypertension in young adults: a multidisciplinary observational study. J Clin Hypertens (Greenwich) 17: 885–894
19. Therneau TM, Grambsch PM (2000) Modeling survival data: extending the cox model. Springer-Verlag, New York
20. Hastie T, Tibshirani R, Friedman JH (2009) The elements of statistical learning : data mining, inference, and prediction. Springer, New York, NY
21. Iki M, Fujita Y, Tamaki J, Kouda K, Yura A, Sato Y, Moon JS, Harano A, Hazaki K, Kajita E, Hamada M, Arai K, Tomioka K, Okamoto N, Kurumatani N (2017) Incident fracture associated with increased risk of mortality even after adjusting for frailty status in elderly Japanese men: the Fujiwara-kyo osteoporosis risk in men (FORMEN) cohort study. Osteoporos Int 28:871–880
22. Cauley JA, Lui LY, Ensrud KE, Zmuda JM, Stone KL, Hochberg MC, Cummings SR (2005) Bone mineral density and the risk of incident nonspinal fractures in black and white women. Jama 293: 2102–2108
23. Stehman-Breen C (2004) Osteoporosis and chronic kidney disease. Semin Nephrol 24:78–81
24. (July 2016) QickFacts; Marshfield, Wisconsin. United States Census Bureau,
25. Komaba H, Taniguchi M, Wada A, Iseki K, Tsubakihara Y, Fukagawa M (2015) Parathyroidectomy and survival among Japanese hemodialysis patients with secondary hyperparathyroidism. Kidney Int 88:350–359
26. Tentori F, Wang M, Bieber BA, Karaboyas A, Li Y, Jacobson SH, Andreucci VE, Fukagawa M, Frimat L, Mendelssohn DC, Port FK, Pisoni RL, Robinson BM (2015) Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. Clin J Am Soc Nephrol 10:98–109
27. Lishmanov A, Dorairajan S, Pak Y, Chaudhary K, Chockalingam A (2012) Elevated serum parathyroid hormone is a cardiovascular risk factor in moderate chronic kidney disease. Int Urol Nephrol 44: 541–547
28. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Wahl P, Gutiérrez OM, Steigerwalt S, He J, Schwartz S, Lo J, Ojo A, Sondheimer J, Hsu CY, Lash J, Leonard M, Kusek JW, Feldman HI, Wolf M, Chronic Renal Insufficiency Cohort (CRIC) Study Group (2011) Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. Jama 305:2432–2439
29. Scialla JJ, Xie H, Rahman M, Anderson AH, Isakova T, Ojo A, Zhang X, Nessel L, Hamano T, Grunwald JE, Raj DS, Yang W, He J, Lash JP, Go AS, Kusek JW, Feldman H, Wolf M, the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators (2014) Fibroblast growth factor-23 and cardiovascular events in CKD. J Am Soc Nephrol 25:349–360
30. Yu N, Donnan PT, Flynn RWV, Murphy MJ, Smith D, Rudman A, Leese GP (2010) Increased mortality and morbidity in mild primary hyperparathyroid patients the parathyroid epidemiology and audit research study (PEARS). Clin Endocrinol 73:30–34
31. Yu N, Leese GP, Donnan PT (2013) What predicts adverse outcomes in untreated primary hyperparathyroidism? The parathyroid epidemiology and audit research study (PEARS). Clin Endocrinol 79:27–34
32. Wetzel J, Pilz S, Grubler MR et al (2017) Plasma parathyroid hormone and cardiovascular disease in treatment-naive patients with primary hyperparathyroidism: the EPATH trial. J Clin Hypertens (Greenwich) 19:1173–1180
33. Shekarkhar S, Foroughi M, Moatamedi M, Gachkar L (2014) The association of serum parathyroid hormone and severity of coronary artery diseases. Coron Artery Dis 25:339–342
34. Maeda S, Wu S, Juppner H, Green J, Aragay AM, Fagin JA, Clemens TL (1996) Cell-specific signal transduction of parathyroid hormone (PTH)-related protein through stably expressed recombinant PTH/PTHrP receptors in vascular smooth muscle cells. Endocrinology 137:3154–3162
35. Benson T, Menezes T, Campbell J, Bice A, Hood B, Prisby R (2016) Mechanisms of vasodilation to PTH 1-84, PTH 1-34, and PTHrP 1-34 in rat bone resistance arteries. Osteoporos Int 27:1817–1826